statins have been widely investigated, and their use is usually recommended in the secondary prevention of acute coronary syndrome (ACS). To investigate the use of statins for the primary prevention of ACS, between April 2004 and February 2005 we enrolled a total of 31 end-stage renal disease patients on MHD, with neither history nor clinical and instrumental signs of earlier major adverse cardiac events (MACEs). We started each patient on atorvastatin (10 mg) daily regardless of serum low-density lipoprotein cholesterol associated with conventional pharmacologic control of blood pressure, serum glucose, and calcium–phosphate balance. During a 4-year follow-up overall 3-year actuarial survival was 67%,[3] compared with a 20–40% 5-year survival reported earlier.[4] Cardiovascular mortality was 12.9%, (4 patients). 'MACE' free' (lethal and non-lethal) 3-year actuarial survival was 53%. Treatment with statins may be considered in the primary prevention of MACEs in hemodialysis patients.

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Response to 'Treatment with statins may be considered in ESRD patients for primary prevention of cardiovascular disease'

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Considering the clinical benefits of statins for primary and secondary cardiovascular event prevention in normal renal function patients, one can assume a similar benefit for patients with chronic kidney disease. Accordingly, Manca-di-Villahermosa's letter[1] reports that a small group of end-stage renal disease patients receiving atorvastatin show low cardiovascular mortality after 3 years of follow-up. However, in the 4-D study—the only randomized placebo-controlled statin trial done to date, which included 1255 patients with type 2 diabetes undergoing hemodialysis—atorvastatin administration was not associated with cardiovascular mortality reduction, which accounts for half the deaths in such patients.[2] Moreover, this occurs independently of the presence or absence of high c-reactive protein levels that are associated with cardiovascular event risk.[3] Reasons for this discrepancy are not evident, as statins exert anti-inflammatory, antioxidant, and lipid-lowering effects as effective as those observed in normal renal function participants. End-stage renal disease patients are at high risk for cardiovascular complications, in whom cardiovascular disease is considered complex and aggravated by coexisting factors, including malnutrition, accelerated atherosclerosis, left ventricular hypertrophy, cardiac fibrosis, and sympathetic overactivity. In the 4-D study, most of cardiovascular deaths were caused by sudden death and not by coronary heart disease.[2] Data for two ongoing large trials (AURORA and SHARP) would help put into perspective statin's beneficial effect in chronic kidney disease with respect to cardiovascular mortality. Apart from this, it has been reported that statin use is associated with sepsis incidence reduction—a major cause of morbimortality in chronic kidney disease.[4] This protective benefit could contribute to total mortality reduction in peritoneal dialysis and hemodialysis patients using statins reported by some observational studies (e.g., DOPPS).[5]

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On vascular calcification prevention with phosphonoformate and bisphosphonates

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To the Editor: Phosphonoformic acid (PFA) is a non-hydrolyzeable inorganic pyrophosphate analog, and it has been used as an experimental inhibitor of renal and

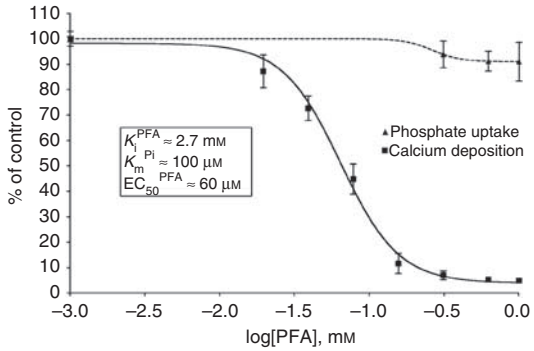

Figure 1 | Effect of phosphonoformic acid (PFA) on inorganic phosphate (Pi) transport and calcium deposition in vascular smooth muscle cells.

intestinal inorganic phosphate (Pi) transport.[1] PFA competitively inhibits type II Na/Pi cotransporters (intestinal NaPi-IIb, and renal NaPi-IIa and NaPi-IIc).[1] Conversely, it is not an inhibitor of type III Pi transporters, namely the ubiquitous Pit-1 and Pit-2, as we have shown[2] and as Professor Giachelli has demonstrated recently in this journal.[3]

PFA successfully prevents Pi-induced calcification of vascular smooth muscle cells (VSMCs; EC_{50} of 60 μM),[4], but it inhibits Pi transport with very low affinity (K_i 2.6 mM)[2] because these cells only express type III Na/Pi cotransporters.[2] Therefore, the mechanism of vascular prevention by PFA should be different from that of Pi-transport inhibition, as we have described recently (Figure 1).

In a recent study,[4] we clarified the mechanism whereby PFA prevents VSMC calcification. We showed that PFA inhibits calcium-phosphate deposition in a process that is independent of any cell activity or metabolism and that is similar to the physicochemical mechanism of bisphosphonate drugs and pyrophosphate.[4] This rationale was already proposed decades ago by several researchers, and it also coincides with a recent study by Prof. O'Neill's group.[5] Therefore, the use of PFA as a tool to inhibit Pi transport in vascular calcification research should be avoided, because the concentrations of PFA that significantly inhibit Pi transport in VSMC also exhibit cytotoxic side effects.[4]

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Response to 'On vascular calcification prevention with phosphonoformate and bisphosphonates'

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Despite the fact that phosphonoformic acid (PFA) is a very weak inhibitor of the type III phosphate transporters present in vascular smooth muscle, its inhibition of calcification in cultured vascular smooth muscle cells (VSMCs) has been used to support a role for phosphate transport in vascular calcification.[1] However, as pointed out by Villa-Bellosta and Sorribas,[2] PFA is also a non-hydrolyzable analog of pyrophosphate (PPi). PPi is a potent, direct inhibitor of hydroxyapatite crystal formation that inhibits vascular calcification *in vitro* and *in vivo*, a property shared by a number of analogs, including bisphosphonates.[3] Not surprisingly, Villa-Bellosta and Sorribas have shown that this is also the mechanism by which PFA inhibits calcification in VSMCs. This is yet another example of a 'specific' inhibitor that, like most 'specific' inhibitors, is not specific.

Subsequent studies using antisense RNA directed against Pit-1 have also shown inhibition of calcification in VSMCs,[4] supporting a role for phosphate transport. However, caution must also be exercised in interpreting these results because VSMCs undergo substantial phenotypic changes in culture and lack the normal elastin matrix, which is the site of medial calcification *in vivo*. Using the whole aorta culture method, we have been unable to duplicate many of the findings in VSMCs related to medial calcification. Thus, the intriguing and potentially important role of phosphate transporters in vascular calcification, although widely cited, remains to be proven in a relevant model.

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